IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Jane Hirsh, Whe-Yong Lo, and Kamal K. Midha

Serial No.: 09/858,016 Art Unit: 1616

Filed: May 15, 2001 Examiner: Gollamudi, Shirmila. S.

For: *PHARMACEUTICAL COMPOSITIONS FOR BOTH INTRAORAL AND ORAL ADMINISTRATION*

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Commissioner for Patents
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Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This is a reply brief to the Examiner's Answer mailed February 8, 2007, in the above-referenced application. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $500, the fee for a Request for Oral Hearing for a small entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

i) whether claims 33-57 are definite as required by 35 U.S.C. §112.

(ii) whether claims 33-39, 41-50, 51-56, are obvious under 35 U.S.C. 103(a) over GB 800,973 to Sterling ("Sterling") in view of U.S. Patent No. 6,140,319 to Powell et al. ("Powell") and further in view of DE 3338978 to Frömming ("Fromming") and U.S. Patent No. 3,898,323 to Fennell ("Fennell").

(iii) whether claims 41, 51, and 54 are obvious under 35 U.S.C. § 103(a) over Sterling, in view of Remington's Pharmaceutical Sciences, 18th Ed. (1990), page 844 ("Remington") and further in view of Fennell.

(iv) whether claims 33-36, 38-39, 43-44, 47-49, 52-53, 55-56, and 49-57 are obvious under 35 U.S.C. 103(a) over U.S. Patent Publication No. 2001/0002999 by Neuser, et al. ("Neuser") in view of U.S. Patent No. 4,661,492 to Lewis et al. ("Lewis") and further in view of U.S. Patent No. 5,686,122 to Liedtke ("Liedtke").

(v) whether claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are obvious under 35 U.S.C. 103(a) over International Publication No. WO 00/35296 by Johnson ("Johnson").

(vi) whether claim 57 is obvious under 35 U.S.C. 103(a) over Johnson in view of U.S. Patent No. 5,310,561 to Jao, et al. ("Jao").

(vii) whether claims 33-43 and 49-57 are obvious under 35 U.S.C. 103(a) over U.S. Patent No. 5,053,032 to Barclay, et al. ("Barclay") in view of U.S. Patent No. 6,200,604 to Pather, et al. ("Pather").

(viii) whether claims 33-57 are obvious under the judicially created doctrine of obviousness-type double patenting, over claims 1-19 of U.S. Patent No. 6,863,901 and claims 1-20 of U.S. Application No. 11/041474.

(7) ARGUMENTS

Appellants affirm all of the arguments made in the Appeal Brief

(a) The Claimed Invention

Medications are typically administered in the prior art orally, intraorally, parenterally by injection, or intravenously, for release at a single site, immediately, continuously, or after a delay. Appellants have devised a method for administering one or more pharmaceutical agents in an effective amount, by both an intraoral and an oral means, in the same composition. The composition comprises two components. The first component is the intraoral component and the second component is the oral component, formulated to be within the first component, so that it is released after the first component, with the first component applied as a film coating or a compression coating around the second component. The pharmaceutical composition for intraoral administration must be capable of sublingual or buccal absorption. Not all drugs are capable of sublingual or buccal absorption. The core can include a signaling system such as flavor particles, color change, gas liberation etc., which can be detected by the patient once the intraoral component is completely dissolve, such that the patient can swallow or chew and swallow the oral component.

(b) Rejection under 35 U.S.C. § 112

Claims 33-57 were rejected under 35 U.S.C. § 112, second paragraph, on the basis that the second oral portion is supposed to be released in the intestine and yet is chewed. This rejection is confusing. Chewable does not mean that release must occur in the mouth. Release is generally interpreted as well the drug is released in a form suitable for uptake. In this case, chewing breaks up drug containing particles, which are swallowed and pass into the small intestine, where uptake occurs.

The Examiner also alleges that claims 1, 41, and 55 lack sufficient antecedent basis for the term "the core". Claim 1 has been canceled. It is assumed that the Examiner is referring to claim 33. Should the claims be found to be otherwise allowable, the claim will be amended as required by the examiner to provide antecedent basis, solely to facilitate prosecution, however, it is believed the claim is clear and fully supported if one looks at the correct base claim.

The Examiner also alleges that "comprises one or more of the outer layers" in claim 37 lack sufficient antecedent basis. This objection is unclear. Claim 37 depends from claim 35, which defines the composition of claim 33 in the form of a tablet or capsule unit dosage form. Claim 37 defines the tablet of claim 33 as a multilayer tablet, wherein the oral component comprises one or more inner layers of the tablet and the intraoral component comprises one or more outer layers of the tablet. The antecedent basis is inherent in the claim itself.

(c) Rejections Under 35 U.S.C. § 103

Claims 33-39, 41-50, and 51-56 were rejected as obvious over Sterling in view of Powell, Fromming and Fennell. Claims 41, 51, and 54 were rejected as obvious over Sterling in view of Remington and Fennel. Claims 33-36, 38-39, 43-44, 47-49, 52-53, 55-56, and 49-57 were rejected as obvious over Neuser in view of Lewis and Liedtke. Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 were rejected as obvious over Johnson. Claim 57 was rejected as obvious over Johnson in view of Jao. Claims 33-43 and 49-57 were rejected as obvious Barclay in view of Panther.

Claims 33-39, 41-50, and 51-56 are not obvious over Sterling in view Powell, and further in view of Frömming or Fennell.

Sterling

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, this having an outer medicinal layer soluble in the mouth. Sterling does not disclose a composition wherein an intraoral portion is a film coating or a compression coating. Sterling describes compositions wherein a drug is **dusted** onto a core of a second drug. As the examiner notes, Sterling does not disclose the claimed drugs nor does Sterling disclose or lead one skilled in the art to drugs which are absorbed sublingually, much less to a teaching that such a drug should be put on the outside of a core of a drug formulated for release and uptake in the small intestine.

Powell

Powell describes the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris. There is no disclosure of intraoral and oral delivery, the need for two routes of delivery, or a means of achieving oral and intraoral delivery.

Fromming

Frömming describes the use of verapamil or gallopamil for sublingual or buccal administration administered in a tablet, a chewable capsule or a spray.

There is nothing leading one skilled in the art to substitute the drugs of Fromming for the drugs of Powell, with the additional teaching that such drugs should be on the outside of the formulation in an effective amount for sublingual uptake.

Fennell

Fennell discloses a composition comprising miraculin and a non-toxic alkaline material. The composition can be powdered, liquid or formed into a tablet. In the coated tablet or powdered form, the alkaline material can form a coating for the tablet. The coating can be applied by compression over the tablet core utilizing a tablet press of it is formed by tumbling the miraculin core in a drum containing alkaline material or into which the said alkaline material is sprayed.

Again, the prior art fails to provide the necessary motivation to combine as appellants have done. The examiner focuses on the chemical action of the drugs of Powell and Fromming being similar but this is irrelevant to the claimed invention, since the missing and critical element is the selection of a drug which is released and taken up sublingually, placed on the outside of a formulation which is swallowed and subsequently absorbed from the small intestine.

Claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are not obvious over Neuser in view of Lewis and further in view of Liedtke.

Neuser

Neuser describes pharmaceutical compositions which can be administered orally and contain a fixed combination of at least one ***locally*** acting analgesic with a rapid onset of action and at least one ***systemically*** acting analgesic with a sustained action. The locally acting analgesic is not absorbed intraorally but is active at the surface it contacts.

Lewis

Lewis describes an analgesic composition in parenteral or sublingual unit dosage form comprising an active dose of buprenorphine and an amount of naltrexone sufficient to prove

aversive to a narcotic addict by parenteral administration but insufficient to compromise the analgesic action of the buprenorphine.

Liedtke

Liedtke describes single dosage **topical** pharmaceutical formulations such as buprenorphine.

No where is there any teaching to put a drug absorbed in the small intestine in a core surrounded by an outer effective amount for sublingual absorption.

Claims 33-43 and 49-57 are not obvious over Barclay in view of Panther.

Barclay

Barclay describes an ***osmotic*** device for delivering a drug into the mouth of a human patient (abstract). The device comprises a wall surrounding a compartment housing, a layer of an agent insoluble to very soluble in aqueous biological fluids such as saliva and a layer of fluid swellable hydrophilic polymer. A passageway in the wall connects the agent with the exterior of the device. The agent is released from the device by the combined actions of fluid being imbibed through the wall into the compartment, producing a solution or suspension containing agent and by fluid being imbibed by the hydrophilic polymer causing it to expand and increase in volume, thereby exerting a force against the solution or suspension which is pushed through the passage way. Example 3 describes an osmotic device containing an overcoat of ibuprofen and HPMC. The overcoat layer is completely removed in 15-30 minutes. In some embodiments, the device can be used to extend the absorption of a drug that might be poorly absorbed throughout certain portions of the GI tract, by administering a predetermined percentage of the drug in the buccal cavity, followed by delivery of the remaining dose in the GI tract (Barclay, column 8, lines 28 to 35).

Pather

Pather describes a pharmaceutical dosage form comprising an orally administerable medicament in combination with an effervescent agent used as a penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa (col. 2, lines 7-11). Panther discloses that the effervescent agent can act to increase the rate and extent of absorption of the active agent by: (1) reducing the mucosal layer thickness and/or viscosity; (2) tight junction alteration; (3) inducing a change in the cell membrane structure; and (4) increasing the hydrophobic environment within the cellular membrane.

Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious over Johnson.

Claim 57 was rejected as obvious over Johnson in view of Jao.

Johnson

Johnson describes a coated chewing gum, wherein the coating contains a medicament or active agent for systemic delivery upon chewing. The core of the chewing gum can also contain an active agent. There is no disclosure of an agent that is released and absorbed intraorally and an agent that is released and absorbed orally (i.e., in the lower gastrointestinal tract) – there is only disclosure of a composition that is released in the mouth and swallowed for absorption in the lower gastrointestinal tract, as well as a second component that may also be swallowed intact for subsequent release and absorption in the gastrointestinal tract.

Claims 33-40, 42-46, and 49-54

Sterling in combination with Powell, Fromming and Fennell

Claim 33 defines a pharmaceutical composition comprising a first intraoral portion and a second oral portion containing a pharmaceutically active ingredient which is released into the intestine after the intraoral portion has disintegrated. Claim 33 requires the second portion be

either a sustained release or a chewable formulation and also, that the pharmaceutical contained therein be released in the intestine. None of the prior art teaches the desirability of a single formulation providing release at two sites and times: intraoral (first) and oral (second), wherein the second site is a sustained release formulation. None of the prior art discusses the problems with first pass metabolism. The claimed subject matter cannot be obvious unless one skilled in the art is led to combine drugs that can be combined, so that one is released first, in the mouth, and absorbed there, followed by a second drug that can be ingested for subsequent absorption lower in the gastrointestinal tract. Many drugs, as discussed in the application, are not absorbed intraorally. It is well established that the mere possibility something may occur is not sufficient to make it obvious. The prior art must lead one to the claimed composition, with the motivation and enablement to make and use it as claimed, with a reasonable expectation of success.

Sterling does not disclose a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level, wherein the active ingredient is as defined in claim 33. Sterling fails to disclose a second component which is either chewable or provides sustained release. Sustained release is where the drug is released over an extended period of time, for example 0.5 to 24 hours (page 23, lines 21-26). Delayed release as described by Sterling, is not the same as sustained release. None of the prior art teaches sustained release.

The Examiner has ***newly alleged*** that "sustained release" is a relative term, and that without any parameters, any time frame can be read on it. Appellants respectfully point out to

the Examiner that one of ordinary skill in the art would not read just any time frame into the term "sustained release", and would understand that the claims differentiates the claimed compositions from immediate release compositions, both terms which are routinely used in the art, and which determine the type/proportion of additives added into the composition. However, the Examiner alleges that Sterling uses 2% alginic acid in the core of the composition disclosed in Sterling, and that alginic acid is a sustained release excipient, citing U.S. Published Application No. 2003/0228361 by Baichwal, et al. ("Baichwal"). ***Appellants respectfully point out that Baichwal has not been made of record during prosecution of this application nor has this rejection been previously raised, so two new references are attached to respond to the new rejection.***

The conclusion drawn by the Examiner from Baichall with respect to Sterling is erroneous. Sterling is not concerned with preparing a sustained release formulation, and so, the Examiner has no basis for concluding that Sterling is using alginic acid for the purpose of providing sustained release. Aliginic acid has many uses, and one of its oldest uses in the pharmaceutical industry is as a disintegrant (aiding in immediate release) (this fact is well known to those skilled in the art, for example, as demonstrated by http://www.pformulate.com/disintegrs.htm). Furthermore, the concentration of alginic acid used in a formulation and the presence/absence of other polymers, determines the function for which it was employed. Alginates in the range of 2-10% are employed as disintegrants; however they are effective for sustained release in the range of 20-50% alone or they can be used at lower concentrations if in combination with other gel forming polymers (please see a review on Alginates for agricultural applications from International Specialty Products, a copy of which is attached). Appellants submit that the attached reference has not been made of record similar to

the new cited reference (U.S. Patent No. 2003/0228361) cited by the Examiner. However, Appellants submit the reference for the sole purpose of rebutting the Examiner's reasoning regarding the disclosure in the new reference cited by the Examiner. The Examiner also alleges that the Examples in Appellants disclosure utilize the sustained release polymer in an amount between 2-8%. The Examiner attention is drawn to the fact that none of the examples use alginic acid. Furthermore, the Examiner's attention is respectfully drawn to page 46 of the present application, wherein hydroxypropylmethyl cellulose is used in a % weight of 30-50%, and on page 54 wherein hydroxypropyl methyl cellulose is used in a %weight of 40-60. These are examples of the preparation of sustained release cores. As disclosed in the present application at least at page 23 line 25 until page 24, line 3, as well as in Baichwal [0067] cited by the Examiner, hydroxypropylmethyl cellulose is a sustained-release polymer. Furthermore, Baichwal discloses the range of the sustained release excipient to be from about 10-60% weight of the final formulation. It is clear from the discussion above and the disclosure in Sterling, that the 2% alginic acid in the core (See the Examiner's Answer on page 23, second paragraph) of the formulation is used as a disintegrant, and a formulation using alginic acid for the purpose of sustained release will contain a much higher concentration of alginic acid. One of ordinary skill in the art from the disclosure in the present application of a formulation for sustained release would not use the concentration of alginic acid employed in Sterling. Therefore, not only is the formulation in Sterling different from that claimed, Sterling actually teaches away from the claimed formulation, because the core as prepared in Sterling is will immediate release (by use of the disintegrant) upon contact with a fluid environment.

With respect to the limitation in the claims that the core of the composition be chewable, the Examiner alleges that since the present application teaches starch and magnesium stearate as

suitable excipients for a chewable formulation, and Sterling teaches starch and magnesium stearate in the core composition, therefore according to the Examiner the composition disclosed in Sterling is capable of being chewed. Whether the drug is capable of being chewed is not the issue here. In order for the composition disclosed in Sterling to anticipate the limitation of being a "chewable formulation", it must be formulated to be chewable, not merely be capable of being chewed. All tablets are capable of being chewed. If the Examiners reasoning were correct, this would mean that all tablets can be classified under chewable formulations. One of ordinary skill in the art understands that chewable formulations are formulations that are meant to be chewed and would recognize that this would affect not only the excipients included in the formulation, but the combination of excipients and for a particular excipient, the concentration, depending on its intended use in the formulation, as discussed for alginic acid for example, above. Nowhere in Sterling is there mention of the intraoral portion of the tablet being chewable. Rather, Sterling repeatedly discloses that the intraoral portion needs to be swallowed (See Sterling, page 1, left column, lines 11-23, page 1, right column, lines 59-83, page 2 right column, lines 86-105). It is evident that the formulation in Sterling is meant to be swallowed, not chewed and therefore, the excipients incorporated in the formulation disclosed in Sterling will be different not only in type, but also, in proportion even for the same excipient.

None of Powell, Fromming, nor Fennell make up for the deficiencies in Sterling. According to the Examiner, the secondary references are relied upon to cure the deficiency of a lack of disclosure of the claimed drugs (Examiner's answer, paragraph spanning pages 21 and 22). Appellants respectfully point out that as discussed above, Sterling is deficient in more than the listed drugs with respect to the limiations of claim 33, and infact, Sterling teaches away from

a formulation which has a sustained intraoral portion. Therefore, a combination of the references does recite all the claim limitations as required by a rejection under 103 (a).

Neuser in combination with Lewis and Liedtke

The references do not disclose each and every element of the claims. The claimed compositions contain a first intraoral and a second oral active agent, wherein the second portion is either a sustained release or chewable formulation. Lewis and Liedtke do not provide the elements missing from Neuser. A combination of Lewis and Neuser as asserted by the Examiner would result in a formulation having as a fast acting component buprenorphine, and as a second component a systemically acting analgesic as listed in Neuser. Neuser requires the first portion be a locally acting analgesic with a rapid onset of action (Neuser, [0001]) and an optimal duration of action lasting 0.5 to 120 minutes (Neuser, [0013]. Neuser further discloses that local anesthetics of this type display their action after less than one minute but have only a short duration of action (Neuser [0002]). As stated in the Appeal Brief, buprenorphine is a long acting drug. Furthermore, buprenorphine does not have a rapid onset of action as required by Neuser. One of ordinary skill in the art would therefore not be motivated to substitute Neuser's anesthetics with buprenorphine as asserted by the Examiner. However, the Examiner asserted in the reply brief (page 33) that Neuser only teaches that it is preferable that the local analgesic have an active time of 0.5-10 minutes, further citing to paragraph [0009] of Neuser wherein is disclosed bupivacaine and mepivacaine whose duration of action the Examiner asserted, is 3-5 hrs and 2-3 hrs respectively. Appellants respectfully point out that with the disclosure in Neuser of the preferred duration of action of 0.5-120 minutes for the immediate analgesic action, one in ordinary skill in the art would not be motivated to use buprenorphine, which has the ability to remain active in some patients for 72 hours and for 24-48 hours typically. Furthermore, Neuser

requires that the locally acting analgesic have a rapid onset of action, within a period of up to 10 minutes (Neuser, [0006]). This is not stated as a preferable upper limit. This ***is*** the upper limit as disclosed in Neuser. The preferable time points are a period of 4 minutes, in particular a period of 1 minute and very particularly, a period of 30 seconds (Neuser, [0006]). Bupivacaine and mepivacaine cited by the Examiner for allegedly having long duration of action however, fall within the catergory as required by Neuser, of drugs with a rapid onset of action. Buprenorphine has an onset of action of 60-120 min. Neuser teaches away from analgesics which have an on onset of action longer than 10 minutes. Buprenorphine falls in this category, thus Appellants maintain that one of ordinary skill in the art would not be motivated to combine Neuser and Lewis as the Examiner has done.

With respect to Liedtke one of ordinary skill in the art would not be motivated to combine the references as Liedtke discloses **topical** formulations, not oral formulations as defined in the claims. However, the Examiner asserted that regardless of the dosage form, the drug will retain its properties, i.e. the property of acting as a local analgesic, irrespective of the local analgesic being formulated into an oral versus topical formulation, and that clearly, buprenorphine can be formulated into oral formulations as taught by Lewis. The Examiner's attention is respectfully drawn to the MPEP §21432.01 wherein is stated that "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)." For reasons already discussed, a skilled artisan will not combine Lewis and Neuser as the Examiner has done. Secondly, Appellants respectfully disagree with the Examiners assertion that the formulation type is irrelevant. The claims require that the pharmaceutical be released in an effective amount. The fact that a compound is an

analgesic does not mean that any and every concentration of that compound will be effective as an analgesic. One of ordinary skill in the art recognizes that formulation type determines the concentration of active ingredient, and therefore, a topical formulation would not necessarily have the same concentration of the same active ingredient, in order to be effective. See also Liedtke, col 1, lines 20-29, wherein is disclosed that transdermal administration of nitroglycerine could not be therapeutically successful, whereas sublingual nitroglycerin is effective. If the Examiner's reasoning is applied in this case, the properties of nitroglycerin are not supposed to change regardless of whether it is in a transdermal or sublingual formulation. Clearly, a disclosure of a topical formulation does make obvious the concentration of drug that would be effective in an oral formulation. None of the cited references disclose a chewable formulation. As previously stated, the fact that a formulation is intended to be chewed is not merely an intended use, it determines what excipients are used and for the same excipient, the concentration used. Accordingly, claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are not obvious over Neuser in view of Lewis and Liedtke.

Claims 33-43 and 49-57 are not obvious over Barclay in view of Pather.

The claimed compositions contain an intraoral portion which rapidly dissolves and is therefore released rapidly after coming in contact with the patient's saliva for immediate absorption in the mouth; preferably within ten minutes. The active agent in the oral portion is released due to dissolution of the carrier or degradation of the sustained release matrix. It is not released by being pushed out a passageway drilled through the core as described in Barclay. The main objective in Barclay is to overcome the problems encountered in buccal delivery of drugs, by making a device for buccal delivery of drugs for an extended period of time (see Barclay, column 4). This actually is teaching away from the presently claimed formulation which

requires that the intraoral portion be rapidly dissolves or disintegrates. However, the Examiner cited to column 8, lines 28-51 of Barclay, stating that Barclay clearly teaches a portion that administers a drug bucally and a second portion that administers the drug to the GI tract. Appellants respectfully point out that the issue is not whether Barclay discloses buccal administration-that is the purpose of Barclay. The issue is that the claims require rapid dissolution or disintegration and therefore rapid release of the active agent in the formulation, whereas Barclay is concerned with the exact opposite of this, providing an osmotic pump that ensures sustained delivery of the active agent in the buccal cavity (see Barclay, col. 4, lines 5-51). Furthermore, the cited paragraph discloses that a predetermined dose may be administered buccally, however, it does not state that it is administered rapidly. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)." (See MPEP §2143.03). The Examiner cited to Example 3 of Barclay which discloses that ibuprofen is overcoated on the device and that generally, the overcoat layer will be completely removed by patient sucking within about 15 to 30 minutes, and alleges that disclosure reads on the limitation in the claims that the intraoral rapidly dissolve or disintegrates. Appellants disagree with the Examiner's allegations for the following reasons: Barclay should be read as a whole; In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Barclay is concerned with sustained buccal delivery. Secondly, as disclosed in Example 3 of Barclay, the device is overcoated with a mixture comprising 20 wt % ibuprofen

and 80 wt % HPMC (hydroxyprolylmethylcellulose, which the Examiner has repeatedly cited in his reply brief as an excipient for sustained release, asserting that the presence of this compound in a composition renders to it the properties of extended release). Thirdly, Example 3 states that the overcoat layer will be removed within 15-30 minutes, not that the active agent will be released within 15-30 minutes. Of note is the fact that said overcoat layer is a mixture of ibuprofen and HPMC in a concentration used for sustained release. This is not a disclosure of dissolution of the intraoral portion, let alone rapid dissolution to release the active ingredient.

Barclay discloses a pharmaceutical device which is very different form the claimed composition, it is unclear how the device can make obvious the claimed composition. Furthermore, Barclay teaches away from a chewable formulation, the device is to be swallowed. Although the claims in a patent application are given their broadest possible meaning, the claims supposed to be read in light of the specification. The present application is not concerned with devices, and Appellants disagree with the Examiner's assertion that the claimed composition reads on Barclay's device. The Examiner relied on Pather to teach the dosage amount of prochlorperazine. However, Panther does not make up for the deficiencies in Barclay. Furthermore, one of ordinary skill in the art would not be motivated to combine Barclay and Pather to arrive at the claimed compositions. Barclay described devices where the drug is release by being pushed put a passageway, which is drilled into the core of the device for sustained delivery of drug to the buccal cavity. The references in combination do not recite all the limitations of the claims. Accordingly, claims 33-43 and 49-57 are not obvious over Barclay in view of Pather.

Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious over Johnson.

The claimed compositions contain an **intraoral** portion that rapidly dissolves or disintegrates immediately upon administration and is immediately absorbed. The second oral portion is located within the intraoral portion and it is released for uptake into the intestine in a therapeutically effective amount, wherein the second portion is either a sustained chewable formulation. Johnson does not disclose a pharmaceutical composition comprising an intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of a pharmaceutical agent. The medication released in Johnson, is released during the chewing period. The requirement that the intraoral portion rapidly dissolve as claimed influences the choice of excipients in which the pharmaceutical is incorporated. Johnson does not disclose a second oral formulation that is in a sustained release or delayed release formulation, with an intraoral portion which is released in the intestine in a therapeutically effective amount. The claimed compositions are designed to be swallowed once the intraoral layer has disintegrated. The medicament included in the chewing gum disclosed in Johnson is meant for absorption in the buccal cavity (Johnson, page 4, lines 1-15). Johnson discloses on page 13, lines 23-25, that there may be a benefit in having a part of the active agent in the chewing gum formulation. Johnson also discloses on page 15, lines 8-13, that one agent may be added to the coat for fast release, and also added to the gum center with, or without encapsulation for slow release. There is no disclosure of a composition with a second oral portion located within the first portion, wherein the second portion is either a sustained release or a chewable formulation, wherein the active agent is released in the intestine in a therapeutically effective amount. The Examiner asserted that Johnson's core is chewable and is capable of being swallowed. Appellants maintain that chewing gums are not normally swallowed. A

person of ordinary skill in the art would not expect that a chewing gum will be swallowed. In order for a composition to qualify as a chewing gum, it must have a gum base, a requirement that is not needed in tablets, whether they are meant to be swallowed or chewed. Although chewing gum formulation can be tableted, this does not mean that such a formulation qualifies as a "tablet" formulation as is routinely used by one of ordinary skill in the art. The chemical components of a chewing gum are different from those of a "tablet", at least with respect to the mandatory requirement for a gum base (see Johnson, page 17, line 24 until page 19, line 9). Furthermore, as disclosed in Johnson, the gum base portion of the chewing gum is retained in the mouth throughout the chew (Johnson, page 17, lines 24-28); it is believed that during the chewing, the active agent remains in the buccal cavity and may be forced or partitioned through the oral mucosa (Johnson, page 6, lines 15-17). The fact that the active agent in Johnson is intended solely for buccal delivery influences the amount/type of the active agent/excipients loaded in the composition. Therefore, Johnson does not disclose a composition with a second oral portion, wherein the active agent is released in the intestine in a therapeutically effective amount, nor enable one of ordinary skill in the art to make such a composition. The Examiner is respectfully reminded that the limitations of the claims are read in light of the disclosure in the specification. As stated in the MPEP §2111 "The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr*., 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004)." Chewable compositions as claimed are not gums. Conversely, the gums disclosed by Johnson are not the same as the claimed chewable compositions that are meant to release their active agent in the intestine. The

Examiner also assets that the claims recite "chewable formulation" and yet Applicants argue that chewing gums are not normally swallowed. Chewable compositions are routinely used in the art, for delivery of agent such as antacids and anti-flatulents. Chewing gums on the other hand are meant to be chewed but not swallowed. A chewing gum is structurally different from a pharmaceutical formulation which is intended to be chewed then swallowed to enable release of the active agent incorporated therein, in the intestine.

Johnson does not disclose the composition of claim 33 in the form of a capsule or tablet (claims 35-36 and 38-39). Johnson does not recite each and every claim limitation, and therefore cannot make obvious the claims. Accordingly, claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious in view of Johnson.

The Prior Art does not disclose each element of the claims

None of the prior art discloses or teaches that the outer portion of the composition must dissolve or disintegrate rapidly to release only the intraoral portion, nor indeed why this would necessary or advantageous. Fennell discloses a film coating but that alone does not mean that it would dissolve or disintegrate rapidly. Indeed, many film coatings are enteric coatings especially designed not to release until after passage through the stomach. Sterling does not disclose a composition wherein an intraoral portion is film coated or coated with a compression coating. Sterling describes compositions wherein the intraoral portion is dusted onto the core. Nether Powell, Fromming, nor Fennell make up for this deficiency.

None of the prior art teach the claimed dosage range for the intraoral component, which is important since larger dosages are unlikely to be absorbed intraorally, as well as the physical limitations on how much of a drug can be incorporated around the core of a second drug which is

to be released orally. This is also not obvious from any of the art, because there is no disclosure of intraoral delivery other than possibly Frömming, but as noted above this is not clear.

None of the prior art teaches that there must be a second component which is orally delivered in a sustained release or chewable formulation. The prior art teaches chewable formulations, but we do not know if this is for intraoral or oral delivery, nor that the drug as described is in a dosage and form suitable for intraoral delivery. Sterling does not teach a chewable formulation. The Examiner has provided no technical reasoning for his assertion that Sterling reads on the chewable formulation as claimed by Appellants. While it might be true that the core in Sterling can be chewed, this does not mean that it is intended to be chewed, nor that it must be a product that is absorbed in the lower gastrointestinal tract. The way a drug product is designed and manufactured affects the bioavailability of the drug. For example, different drug products that contain the same active ingredient may have different bioavailability depending on differences in the inactive ingredients even if they are administered in the same way (for example as a swallowable tablet). The rate of dissolution of a solid drug form may also affect absorption. The consistency of a tablet meant to be chewed is different from that of a tablet meant to be swallowed whole; chewing increases surface area and rate of dissolution of the drug (please see Johnson, page 2, line 22, until page 3, line 19). Furthermore, a tablet that is intended to be chewed would include sweetening and flavoring agents which help to improve patient compliance, something that would not be of concern to the manufacturer, if the drug were intended to be swallowed whole. Therefore, a drug formulation that is intended to be swallowed does not inherently disclose a chewable formulation because they have very different characteristics.

In summary, none of the prior art discloses the general concept of a two component formulation for initial intraoral delivery followed by oral delivery; a rapidly disintegrating or dissolving coating over an intraoral drug, the selection of a drug for intraoral delivery in a dosage range of between 1 and 50 mg, nor the combination with a sustained release or chewable second component for oral delivery. Absent motivation to combine as appellants have done, the claimed composition would not be obvious from the cited art.

Claim 37

None of the cited art discloses multilayer tables with multiple layers of an intraoral and/or oral component.

Claims 41 and 50

Claim 41 differs from claim 33 by requiring that the drug to be delivered intraorally is either as listed in claim 33 or has a molecular weight not exceeding 350 daltons, and requires either an effervescence or pharamaceutically acceptable signaling system between the two components.

Claims 41 and 56 are not obvious over Sterling in view Powell, and further in view of Frömming or Fennell.

Sterling does not disclose a pharmaceutical composition with an active ingredient having a molecular weight not exceeding 350 daltons, or an active ingredient selected from the ingredients listed in claim 41, being present in an amount between 1 micrograms and 50 mg. Sterling does not disclose a pharmaceutical composition comprising a pharmaceutically acceptable effervescent agent which generates effervescence or a pharmaceutically acceptable signaling system, located between the first intraoral component and the second oral component, which is detectable by the patient upon substantial release of the pharmaceutically active

ingredient in the first intraoral component when contacted with salivary fluid as defined by claim 41. Sterling also does not disclose a composition wherein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core. Neither Powell, Fromming, nor Fennell make up for this deficiency.

None of the prior art discloses the general concept of a two component formulation for initial intraoral delivery followed by oral delivery; a rapidly disintegrating or dissolving coating over an intraoral drug, the selection of a drug for intraoral delivery in a dosage range of between 1 and 50 mg, nor the combination with a sustained release or chewable second component for oral delivery. None of the art discloses placing an effervescent agent in the intraoral component. None of the art discloses placing a signaling means between the intraoral and oral components. Thus, there would is no motivation to combine or modify as required to arrive at the claimed compositions.

Claims 43 and 44

Claim 43 requires the second oral component to be a sustained release formulation; claim 44 requires sustained release over a period of 0.5 to 24 hours.

None of the cited art discloses a second component in a two component formulation which provides sustained release as required by claims 43 and 44. Sustained release is defined as where the drug is released over an extended period of time, for example 0.5 to 24 hours (page 23, lines 21-26). Delayed release which is taught by Sterling, is not the same as sustained release. None teach sustained release except in the case of an osmotic device, which is not part of a two component system where there is a first intraoral component, nor any teaching that would lead one to combine two such component.

Claims 45 and 46

None of the cited art discloses a two component system wherein the second component is for oral delivery and provides for delayed release. There is no motivation to modify and combine any of the cited art as appellants have done to create a single formulation that can deliver drug immediately intraorally, then release much later a second component after passage through the stomach.

Claim 47

None of the cited art discloses a pharmaceutical composition with two portions wherein the second portion is chewable, and comprises at least one pharmaceutically acceptable excipient suitable for a chewable medication and a flavoring agent, nor any motivation to make such a combination.

Claim 48

Claim 48 requires the first intraoral component to disintegrate or dissolve within 10 minutes, when the composition is contacted with saliva during intraoral administration. Claim 49 requires the second oral component to remain intact until the intraoral administration of the first intraoral component has been delivered.

The examiner has cited no art teaching the criticality of a two component system wherein the first component dissolves or disintegrates within 10 minutes, nor where the second component must remain intact after the first component is delivered. Indeed, these features are integral to a two component delivery system releasing drug at different places and different times, and is simply not discloses by nor obvious from any aspect of the cited prior art. The examiner has done nothing more than generally group all claims together and ignore the features

that make this such a desirable system for those individuals in need of combined drug therapy, where an initial very rapid onset is essential, followed later by delivery of drug orally.

Claim 53

The examiner has cited no art disclosing the claimed dosage range of one to 50 mg, much less the claimed range of 10 to 30 mg of claim 53, for a drug to be delivered intraorally. The prior art fails to recognize the desirability or reason one would deliver initially a first component intraorally, that requires drugs that chemically can be absorbed intraorally, as well as a dosage that can be absorbed intraorally. The prior art is completely silent on either of these important claim limitations.

Claims 55-57

Claims 55-57 define a process for making the formulation of claim 33.

The same arguments made with respect to the formulations are equally applicable here. Sterling does not disclose a process for preparing a pharmaceutical composition in unit dosage, comprising two portions wherein the first is an intraoral portion which disintegrates to release a pharmaceutically effective amount of at least one active ingredient which is absorbed intraorally due to the chemical composition and dosage and a second portion which is released and absorbed within the lower gastrointestinal tract from either a sustained release or chewable formulation.

None of Powell, Fromming, nor Fennell make up for the deficiencies in Sterling. According to the Examiner, the secondary references are relied upon to cure the deficiency of a lack of disclosure of the claimed drugs (Examiner's answer, paragraph spanning pages 21 and 22). The Examiner's answer on page 22 second paragraph also indicates that the Examiner depended on Fennell to make up the deficiency of the coating methods. Appellants respectfully point out that as discussed above, Sterling is deficient in more than the listed drugs with respect

to the limiations of claim 33, and in fact, Sterling teaches away from a formulation which has a sustained intraoral portion. Therefore, a combination of the references does recite all the claim limitations as required by a rejection under 103 (a). Furthermore, there would be no motivation to combine the references as the Examiner has done. The motivation to combine must come from the references cited. Even if a skilled artisan combined the references as the Examiner has done, they would not arrive at the claimed process for the same reasons discussed under claims 33-40, 42-46 and 49-54.

Claims 41, 51, and 54 are not obvious over Sterling in view of Remington and Fennell.

Claims 41, 51, and 54, Sterling and Fennell, are discussed above.

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, this having an outer medicinal layer soluble in the mouth. Sterling does not disclose a pharmaceutical composition comprising a pharmaceutically acceptable effervescent agent which generates effervescence located between a first intraoral component and a second oral component, which is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid. Sterling does not disclose a composition wherein the intraoral portion is present between 1 micrograms and 50 mg. Sterling also does not disclose a composition where the intraoral portion is a film coating applied to the core or a compression coating compressed around the core.

Remington states that nitroglycerin has a molecular weight of 227.09 and that the dose of nitroglycerin is between 1 mg and 0.15-0.6 mg for buccal tablets and sublingual tablets, respectively.

Fennell describes a composition for rendering sour tasting foods sweet tasting comprising miraculin glycoprotein obtained from the ripe fruit of *Synsepalum dulcificum* and a non-toxic alkaline material. The composition is placed in the mouth 1-2 hours before ingesting sour food.

Remington and Fennell do not disclose the claim elements missing from Sterling. One of ordinary skill in the art would not be motivated to combine Sterling and Remington and/or Fennell to make a two component system, much less one containing either an effervescent material in an outer coating or a signaling system between the two components, nor would one achieve the claimed composition even if the prior art were combined. Fennell describes a taste masking composition which is ingested before ingesting sour-tasting foods. The taste masking composition neutralizes mouth acids and coats the tongue. Fennell does not disclose or suggest coating a composition containing an intraoral component and an oral component as defined in claims 41, 51, and 54. Therefore, Claims 41, 51, and 54 are not obvious over Sterling in view of Remington and Fennell.

Claim 57 is not obvious over Johnson in view of Jao.

Claim 57 depends from claim 55 which defines a process for the preparation of a composition containing a first intraoral portion and a second oral portion, wherein the second oral component is a tablet core or at least one layer of a multi-layer tablet or an uncoated capsule, wherein the oral portion is released in the intestine after the intraoral portion has distintegrated, wherein the oral portion is either a sustained release or chewable formulation. Johnson describes chewing gums, not capsules or tablets. Jao describes a dosage form containing a wall that surrounds a lumen comprising the drug, a driving means for delivering the drug, and a rate controlled exit means. One of ordinary skilled in the art would not be motivated to combine the chewing gums of Johnson with the dosage form described in Jao. Johnson describes a

composition which is chewed, wherein the gum base which can contain an active agent remains in the mouth during the chew. A combination of Johnson and Jao as proposed by the Examiner that would lead to a composition that is swallowed, and would render the chewing gum disclosed in Johnson unsatisfactory for its intended purpose, which is that the chewing gum is supposed to be chewed such that the active agent is released in the buccal cavity. The references, in combination, do not disclose each and every element of claim 57 nor the motivation to combine.

(d) Double Patenting Rejection

Claims 33-57 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,863,901 and claims 1-20 copending U.S.S.N.. 11/041,474. In response, Appellants will file a terminal disclaimer to overcome the double patenting rejection upon indication that the claims are otherwise allowable and assuming that the rejection is maintained in view of the status of the claims in U.S.S.N. 11/041,474 at the conclusion of the appeal.

(e) Conclusion

For the foregoing reasons, Appellants submit that claims 1-57 are definite under 35 U.S.C. 112, and non-obvious over the cited art, alone or in combination. The prior art fails to disclose the elements of, and the motivation to combine, as appellants have done, with a reasonable expectation of success, a formulation that provides in a single convenient and economical formulation:

A first component that is rapidly released in the mouth, where the drug is in a dosage (one to 50 mg or 10 to 30 mg) and is chemically able to be rapidly absorbed intraorally, and

A second component that is released and absorbed in the lower gastrointestinal tract following oral administration, which can be in a sustained or delayed release formulation,

which can include within the first component effervescence agents to increase rate of dissolution and uptake of drug, or a signaling mechanism to tell the individual the first dose has been delivered and the second component can now be swallowed.

Respectfully submitted,

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